# EXHIBIT 53

# Free Executive Summary

## Asbestos: Selected Cancers

Committee on Asbestos: Selected Health Effects
ISBN: 0-309-10169-7, 394 pages, 6 x 9, paperback (2006)

# Executive Summary

## INTRODUCTION

The use of asbestos in many products surged during the 20th century, and asbestos exposure continues despite a sharp reduction in production since the 1980s. Asbestos is an established cause of mesothelioma, an uncommon cancer that arises in the mesothelial cells lining the chest and abdominal cavities, and of lung cancer. It also causes non-malignant respiratory diseases, including asbestosis, a fibrotic disorder of the lung. In addition, the findings of some epidemiologic studies of asbestos-exposed workers have suggested that exposure to asbestos may increase risk of other cancers. This Institute of Medicine committee was charged with evaluating the evidence relevant to the causation of cancers of the pharynx, larynx, esophagus, stomach, and colon and rectum by asbestos and with judging whether the evidence is sufficient to infer a causal association. The specific charge follows:

> The Institute of Medicine's (IOM) Board on Population Health and Public Health Practices will oversee a study that will comprehensively review, evaluate, and summarize the peer-reviewed scientific and medical literature regarding the association between asbestos and colorectal, laryngeal, esophageal, pharyngeal, and stomach cancers. Based on its examination and evaluation of the extant literature and other information it may obtain in the course of the study, the committee will determine if there is a causal association between asbestos and colorectal, laryngeal, esophageal, pharyngeal, or stomach cancers.

The committee's charge was drawn directly from Senate Bill 852, the Fairness in Asbestos Injury Resolution (FAIR) Act.

## COMMITTEE APPROACH

To address the charge, a multidisciplinary committee was appointed by IOM that included experts in biostatistics, epidemiology, mineralogy, oncology, toxicology, and cancer biology. The committee interpreted its charge as requiring a comprehensive and systematic

review of evidence on the cancer risk posed by asbestos at the specified sites in humans and in experimental animals. The committee also identified a need to review evidence related to the biologic plausibility of a causal association between asbestos and cancer at the designated sites. Relevant issues included the doses of asbestos fibers reaching the organs, persistence of fibers at the sites, potential interactions with target cells, and plausible mechanisms of carcinogenesis by asbestos fibers at the sites.

The committee was aware that fiber type may be a determinant of risk of developing mesothelioma (and possibly lung cancer) following asbestos exposure. The committee considered whether it should evaluate asbestos-associated risk for the designated cancers in terms of exposure to specific fiber types. In light of the almost universally mixed nature of actual occupational exposure, however, there was not sufficient evidence to have carried out such a review for the selected cancer sites. Consequently, the committee's report describes the level of causal inference in relation to asbestos, without specifying the type.

Accordingly, the committee undertook a systematic review of the available human and toxicologic evidence, setting up a uniform approach for reviewing the full body of relevant epidemiological literature and for abstracting and synthesizing study results. The epidemiologic evidence comes from cohort (follow-up) studies of occupationally exposed persons and from case-control studies of the cancers that assessed occupational exposures as risk factors. The cohort studies generally addressed cancer mortality, and the case-control studies mostly considered incident cases. The studies were further classified by the method of exposure assessment. The results of the studies were then abstracted into a database for descriptive analysis and summary with the technique of quantitative meta-analysis. The units of input for the meta-analysis on each selected cancer site were the most comprehensive risk estimates available on discrete study populations, so a single citation might generate more than one datum (such as separate results for men and women), whereas only the final follow-up results would be used for a series of publications on the same occupational cohort. The meta-analysis on each data set yielded a summary estimate of cancer risk at the anatomical site associated with asbestos exposure with a confidence interval that accounts for sampling variation within each study and for variation in relative risk among studies. The committee also reviewed the toxicologic literature and the extensive experimental literature on carcinogenesis by asbestos fibers. It addressed the mineralogic and chemical characteristics of asbestos for their relevance to carcinogenicity in the organs of interest. The committee consulted experts on those topics through presentations at its meetings.

Because the committee's charge requires a determination of whether asbestos causes cancer at the specific sites, the committee considered various guidelines for causal inference and terminology for classifying the strength of evidence in support of causation. Its review of approaches led to the uniform application of guidelines for causal inference based on the widely applied criteria or guidelines proposed by Austin Bradford Hill and the similar criteria long used in the reports of the US surgeon general on smoking and health. The criteria for causal inference include consistency, strength of association, temporality, and the coherence or plausibility of the association. The committee selected a four-level classification of the strength of evidence for causal inference, classifying the evidence as *sufficient*, *suggestive*, or *inadequate* to infer causality or suggestive of *no causal association*. For the purpose of its charge, designating an

association of asbestos with cancers of the designated sites as causal, the committee required the evidence to reach the level of *sufficient*.

The topic of asbestos and cancer has many facets, including the influence of fiber type on risk and the interactions of asbestos with other factors that produce cancer at the same sites, such as tobacco-smoking for cancer of the larynx. The committee did not consider the issue of fiber type, which was not included in its charge; it did consider information on the combined effect of asbestos with other risk factors when such information was available. The committee also did not attempt to quantify the risk of cancers at the selected sites in relation to magnitude of exposure – a potentially extensive effort that was also beyond its charge.

## COMMITTEE FINDINGS

The committee reviewed the evidence from epidemiologic studies and from toxicologic investigations, both animal and in vitro, specifically for each cancer site. The reviews of the evidence related to mineralogy of asbestos and to its carcinogenicity were considered to be generally relevant for all sites, particularly in regard to the causal criterion of coherence or biologic plausibility.

There has been ongoing discussion as to whether there is an absolute difference in the toxicity of the major fiber types, serpentine and amphibole, and whether only amphibole fibers have carcinogenic potential, particularly for mesothelioma, the neoplasm for which the evidence is most suggestive of a difference in risk by fiber type. Recent reviews suggest that, rather than having no carcinogenic activity, chrysotile has a generally lesser degree of potency than amphibole fiber and that the various types of amphibole fiber have differing potency in the extent of their biological activity. With regard to fiber characteristics, the committee noted that several physical and chemical factors may contribute to a mineral particle's potential to induce a pathogenic response. These characteristics differ for serpentine (or chrysotile) and amphibole fibers and may be relevant to their relative carcinogenicity. Many of the properties would be expected to influence how a mineral interacts with biologic fluids under the conditions in the various organs under consideration. Although these properties have been investigated in simplified systems and their potential relevance in processes in natural environments is clear, their roles in mineral-induced pathogenesis of cancer or other diseases have not been extensively studied in the integrated context of whole animals. Size and shape are relevant because they determine site of deposition and also influence interactions with cells. Dissolution may also be relevant because it removes the fibers, but introduces the materials in the fibers, such as metals, into the surrounding fluid with the potential for interaction with target cells. Surface-induced oxidation-reduction is another catalytic pathway that may contribute to carcinogenesis. Ion exchange between the surfaces of the fibers and the surrounding liquid may affect neighboring cells. How these factors play out in terms of producing disease in humans under conditions of real occupational exposure, however, has not been fully studied.

Although there has been little systematic investigation of dispersion of asbestos fibers to extrapulmonary tissues, they do reach the organs covered by the charge. Inhaled materials deposit throughout the respiratory tract, which extends from the nose and mouth to the alveoli, the lung's air sacs. The sites of deposition vary by fiber size; inhaled fibers pass through the pharynx and larynx with the possibility of deposition there. Fibers deposited in the lung are

cleared by the mucociliary apparatus, and swallowing of asbestos-containing mucus causes it to pass through the gastrointestinal tract and can lead to potential exposure of the esophagus, stomach, and colon and rectum to asbestos fibers. Encapsulated fibers, known as asbestos bodies, are routinely found in the respiratory tissues of asbestos-exposed individuals; although they have not been systematically sought in other organs, there have been some reports of finding asbestos bodies in extrapulmonary tissues, including the portions of the gastrointestinal tract addressed in this report.

The biologic effects of asbestos fibers depend on their physicochemical properties, dimensions, and deposition and persistence at target sites. On the basis of rodent models of lung cancer and malignant mesothelioma, fiber carcinogenicity is correlated with increased cell proliferation, inflammation, and fibrosis in the lungs and pleura. Several mechanisms have been proposed for the biologic activity of asbestos fibers observed in in-vitro and animal-model systems. Long asbestos fibers that are incompletely phagocytized stimulate production of reactive oxygen species that induce DNA damage, oxidant stress, and activation of cell-signaling pathways and lead to cell proliferation. Long asbestos fibers have been shown to interfere physically with the mitotic apparatus and produce chromosomal damage, especially deletions. Asbestos fibers may also directly produce physical injury of target cells and tissues that is repaired by compensatory hyperplasia. There is strong epidemiologic and experimental evidence that asbestos fibers and cigarette smoke are cofactors in the development of lung cancer. Other potential cofactors in malignant mesothelioma are chronic inflammation and viruses (such as SV40). The applicability of these direct and indirect mechanisms of asbestos carcinogenesis to cancers that develop at extrapulmonary sites considered in this report is uncertain.

The committee considered animal-bioassay studies in which animals were administered asbestos by inhalation and the occurrence of cancer was measured. Many studies of that general design have been carried out, but they were directed largely at investigating cancer of the lung and mesothelioma, so only those with comprehensive histopathologic examinations were considered relevant. Among the more limited number of studies with oral administration, the committee found several involving exposure of animals to asbestos fibers mixed into their food particularly relevant. However, the utility of these models for the sites of concern is uncertain.

In addressing its charge, the committee considered both general evidence related to carcinogenicity and site-specific epidemiologic evidence. The committee's reviews and conclusions by site are summarized below. In the following, the relative risk (RR) quantifies the risk of cancer among those exposed to asbestos relative to those not exposed. An RR greater than 1.0 indicates that estimated risk was higher among people who have been exposed, and an RR less than 1.0 indicates that estimated risk was lower among those exposed. An RR of 1.0, sometimes referred to as the null value, corresponds to equal risk in the two groups. The confidence interval (CI) at a given "level of significance" provides an indication of statistical uncertainty.

## Pharyngeal Cancer

The committee reviewed six case-control studies of pharyngeal cancer, four of which had exposure assessments of high quality or adjusted for confounding, and the findings on 16 cohort populations. Although the information from the case-control studies was very sparse, the aggregated risk estimate for any asbestos exposure was modest and similar to that for the more numerous cohort studies. The available data did not suggest the presence of a dose-response relationship. In considering the plausibility of a causal association between asbestos exposure and pharyngeal cancer, the committee noted that the epithelium of the oropharynx and hypopharynx differs from that of the respiratory epithelium, although squamous-cell cancers predominate among tumors of the pharynx. The combination of asbestos exposure and tobacco-smoking is an established risk factor for lung cancer, but for pharyngeal cancer only a single case-control study has addressed asbestos exposure as a cofactor with tobacco-smoking. No increase in pharyngeal tumors has been observed in animals exposed chronically to asbestos either by inhalation or by oral feeding.

Although several cohort studies and the larger, better-designed case-control studies suggest an association between asbestos exposure and pharyngeal cancer and asbestos, overall the epidemiologic evidence is limited and biological plausibility has some uncertainty for this site. *Consequently, the committee concluded that the evidence is* ***suggestive but not sufficient,*** *to infer a causal relationship between asbestos exposure and pharyngeal cancer.*

## Laryngeal Cancer

The evidence base for asbestos exposure and laryngeal cancer included more case-control studies (18) than were available for other cancer sites considered by the committee, and the number of cohort populations (35) was similar to the number informative for stomach or colorectal cancer. Subjects in the studies had been exposed to asbestos in a wide array of industries and occupations in North America, and South America, Europe, and Japan. Many of the case-control studies collected data that permitted confounding by tobacco-smoking and alcohol consumption to be addressed. Several case-control studies examined the association between asbestos exposure and laryngeal cancer, stratifying on tobacco use, which might potentially interact with or modify the association of asbestos exposure with risk of laryngeal cancer. The committee also reviewed four experimental studies in which rodents were exposed over much of their lifetime to high concentrations of asbestos through inhalation.

The committee found consistency of findings among the epidemiologic studies. Asbestos exposure was associated with increased risk of laryngeal cancer in all the nine larger cohort studies and in meta-analyses of the cohort and case-control data. Some evidence of a dose-response relationship was seen in both the cohort and case-control studies. There was no consistent evidence of confounding in case-control studies that reported both age- and multivariate-adjusted RR estimates, and the two studies stratified on asbestos exposure and smoking status suggest synergism between the two factors.

The committee found several bases for considering that asbestos could plausibly cause laryngeal cancer. The larynx, like the lung, is anatomically in the direct path of inhaled asbestos fibers. Inflammation or damage to the vocal cords could disrupt laminar airflow and predispose to the deposition and accumulation of asbestos fibers in the larynx. Squamous-cell carcinomas of the lung and larynx exhibit certain histologic and clinical similarities; cancers at both sites arise from the respiratory epithelium in regions of squamous metaplasia and dysplasia. Tobacco-smoking is the most important risk factor for both sites, and asbestos exposure is an established cause of lung cancer. Tobacco-smoking may lead to laryngeal damage and increased potential for asbestos fibers to deposit in the trachea. Alcohol consumption is also a recognized risk factor for laryngeal cancer, with heavy consumption synergizing markedly with smoking. Together with smoking and drinking, accumulation of asbestos fibers could produce chronic irritation or inflammation, accelerating the progression of neoplasia. However, no clinical data document the accumulation and persistence of asbestos fibers in the larynx, and there is a lack of experimental support from animal studies.

Considering all the evidence, the committee placed greater weight on the consistency of the epidemiologic studies and the biologic plausibility of the hypothesis than on the lack of confirmatory evidence from animal studies or documentation of fiber persistence in the larynx. *The committee concluded that the evidence is **sufficient** to infer a causal relationship between asbestos exposure and laryngeal cancer.*

## Esophageal Cancer

Both case-control and cohort studies of esophageal cancer were reviewed, but the available body of evidence was limited. Only three case-control studies met the criteria for inclusion, so there were too few for meta-analysis. There were more cohort populations with relevant results, although the number of cases was often small. The mortality studies did not distinguish between histologic subtypes; if there were specific asbestos-subtype associations, the overall grouping of esophageal cancers would tend to obscure them. In assessing biologic plausibility, the histologic type of cancer, potential dose to the target tissues, and possible mechanisms were considered.

The three case-control studies did not have consistent results, and the number of exposed cases was generally small. Two incorporated adjustment for tobacco-smoking and alcohol consumption. One observed a small excess risk but did not find evidence of a dose-response relationship, and the other found no evidence of an excess. A third, older study found an excess, but it was based on a single case, and so was difficult to interpret. Few cohort studies presented data explicitly on esophageal cancer, because of the rarity of the disease, and their statistical precision was often low. The results for the 25 cohort populations with information on esophageal cancer were mixed. The summary RR computed from the cohort studies was 0.99 (95% CI 0.78-1.27). Although some studies did observe excess risks, overall there was little consistency in the epidemiologic data. Six animal-feeding studies did not find an association with esophageal cancer, and there is no other experimental evidence that asbestos fibers act as a direct or indirect carcinogen specifically in the esophagus.

Some studies have found an association between asbestos exposure and esophageal cancer, but the overall results of epidemiologic studies are mixed. In addition, what little evidence there is from animal experiments about asbestos's carcinogenic potential specifically on esophageal tissues does not support biological activity at this site. *The committee concluded that the evidence is **inadequate** to infer the presence or absence of a causal relationship between asbestos exposure and esophageal cancer.*

### Stomach Cancer

In its final dataset, the committee considered 42 occupational cohorts and five population-based case-control studies that provided data on stomach cancer risk. Overall, the occupational cohorts consistently, although not uniformly, suggested risks increased above risks in the general population (RR=1.17, 95% CI 1.07-1.28). The results of case-control studies were less consistent (RR=1.11, 95% CI 0.76-1.64), and suggested neither increased nor lower-than-expected risks associated with asbestos. Considering just the cohort studies, the committee noted that observed risk increases were modest. There were also somewhat consistent patterns supportive of dose-response relations, although trends were not especially strong. Six lifetime feeding studies of asbestos in rodents provided no evidence that asbestos fibers act as a direct or indirect carcinogen in the stomach.

The most frequent histologic type of stomach cancer in western countries is adenocarcinoma, which is most commonly associated with *Helicobacter pylori* infection and inflammation. Tobacco-smoking is also a risk factor for stomach adenocarcinoma. The potential role of asbestos fibers as a cofactor with established risk factors has not been investigated experimentally or epidemiologically. Asbestos bodies have been identified in the stomach and in other sites in the gastrointestinal tract and in other organs. The possibility that asbestos fibers could accumulate at sites of mucosal injury and ulceration has not been explored. There is no experimental evidence from animal toxicology studies that asbestos fibers act as a direct or indirect carcinogen in the stomach.

Overall, the epidemiologic studies revealed fairly modest risk increases and somewhat fragmentary evidence of a dose-response relationship. Animal experimentation has not provided supportive evidence of causation, although the potential for asbestos fibers to accumulate at sites of stomach mucosal injury lends some mechanistic support to potential carcinogenesis. *The committee concluded that the evidence is **suggestive but not sufficient** to infer a causal relationship between asbestos exposure and stomach cancer.*

### Colorectal Cancer

The committee evaluated the overall evidence on colorectal cancer because its charge addressed cancers of the colon and rectum together. The evidence thus included studies providing information on the two sites separately and studies reporting on colorectal cancer overall. Case-control studies of colon or rectal cancers included four studies in which the two outcomes were considered in a single category of colorectal cancer, six studies of only colon

cancer, and one of only rectal cancer. In addition, 41 occupational cohorts were reviewed, almost all of which had the necessary information to derive a combined risk estimate for colon and rectal cancers.

There was some inconsistency among the 13 RRs reported from the case-control studies (aggregate RR=1.16, 95% CI 0.90-1.49), and findings from many of the studies were inconclusive. Although most of the estimated RRs were greater than 1, two of the studies had lower estimated risks for those exposed to asbestos. The case-control study with the most detailed assessment and analysis of asbestos exposure did not find an association between exposure to asbestos and the risk of colorectal cancer. In contrast, the occupational-cohort studies more consistently, although not uniformly, suggested increased risks of colorectal cancer in exposed people than in the general population (RR=1.15, 95% CI 1.01-1.31).

The summary estimate of association from the case-control studies was similar to that from the cohort studies, but the CI was wider, and evidence of a dose-response relationship in the case-control studies was lacking. The overall observed risk estimate from cohort studies was modestly increased, although it had 95% CI that just excluded 1.0 and some evidence of a dose-response relationship.

There was only limited information available relevant to biologic plausibility. Colorectal tumors in humans are most commonly adenocarcinomas that arise in polyps. Multiple risk factors are associated with colon cancer, including familial predisposition, age, obesity, physical inactivity, and inflammatory bowel disease. The potential role of asbestos fibers as a cofactor has not been investigated in epidemiologic or experimental studies. Asbestos bodies and asbestos fibers have been identified in the colon, including for a small cohort of asbestos workers who had colon cancer. Animal models have failed to produce colon or colorectal cancer even studies that involved high-dose feeding of asbestos to rodents. However, studies employing high-dose feeding of chrysotile asbestos to rats did produce benign adenomatous colonic polyps, a precursor to the most common form of colon cancer in humans.

The committee concluded that the evidence is **suggestive but not sufficient** to infer a causal relationship between asbestos exposure and colorectal cancer.

## CLOSING COMMENTS

The committee was charged with reviewing evidence on a widely used material that is known to cause respiratory malignancy. Asbestos has been extensively investigated, epidemiologically and experimentally, as a cause of mesothelioma and lung cancer. However, its potential to cause malignancy at other sites that may also receive a substantial dose of asbestos fibers has not been as extensively investigated.

The committee considered the existing evidence from in vitro and animal experimentation to gain an understanding of mechanisms of carcinogenesis that might plausibly apply to the tissues in question and to determine the extent of toxicologic support for the development of cancers at the specified sites following asbestos exposure. Much of the information reviewed by the committee came from cohort studies of workers that focused on

investigating respiratory effects and that reported information on risks of other diseases, including the cancers covered by this committee's charge, only incidentally. Other evidence came from case-control studies that were directed at the causes of the cancers of interest but that were not specifically designed to address asbestos exposure, and their exposure assessments were of varied quality.

Table ES.1 provides a distillation of the committee's findings about whether asbestos is a causal factor for cancers at the five sites indicated for evaluation in the committee's charge and the FAIR legislation.

The committee's review identified limitations of the available evidence and the resulting uncertainty in its conclusions. Although the committee was not charged with developing a research agenda to address the information gaps, its review indicated many research needs. Studies directed at doses of fibers received by organs other than the lung are needed; mechanistic studies directed at these organs could be a useful complement to work on respiratory carcinogenesis by asbestos fibers. Studies involving animal models with high risk of cancer at the designated sites might also be considered. Consideration should be given to approaches to strengthen the epidemiologic information on asbestos exposure and risk of cancer at the sites in the committee's charge. Information might be gained from further follow-up of some of the cohorts of asbestos-exposed workers; however, the committee is concerned that further study of these cohorts maybe impossible because most were initiated decades ago and their records may not have been maintained. Some effort might be made to determine whether key cohorts could be followed up or new studies on potentially informative populations started.

[INSERT TABLE ES. 1]

[END OF EXECUTIVE SUMMARY]

**TABLE ES.1** Causal association between specified cancer and asbestos

| Cancer | Evidence for presence or absence of causal relationship to asbestos |
|---|---|
| Laryngeal | Sufficient |
| Pharyngeal | Suggestive but not sufficient |
| Stomach | Suggestive but not sufficient |
| Colorectal | Suggestive but not sufficient |
| Esophageal | Inadequate |

# Asbestos: Selected Cancers

Committee on Asbestos: Selected Health Effects
Board on Population Health and Public Health Practices

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THE NATIONAL ACADEMIES PRESS
Washington, D.C.
**www.nap.edu**

**THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001**

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by Contract N01-OD-4-2139 between the National Academy of Sciences and the National Institutes of Health. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number 0-309-XXXXX-X (Book)
International Standard Book Number 0-309- XXXXX -X (PDF)
Library of Congress Control Number: 00 XXXXXX

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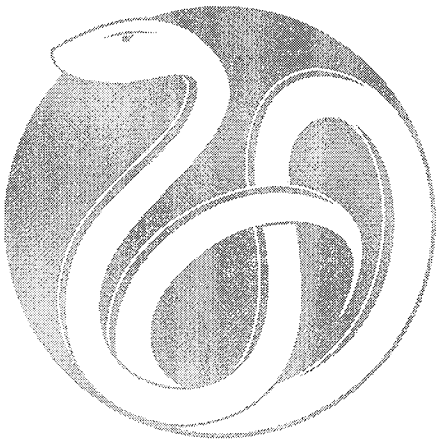
Printed in the United States of America.

The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

*"Knowing is not enough; we must apply.*
*Willing is not enough; we must do."*
—Goethe



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The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Wm. A. Wulf are chair and vice chair, respectively, of the National Research Council.

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## REVIEWERS

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Paul D. Stolley,** University of Maryland, School of Medicine, Baltimore, Maryland, and by **Edward B. Perrin,** University of Washington, Seattle, Washington. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author committee and the institution.

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